PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ABL-013-PCT2	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/BE 03/00193	International filing date *(day/month/year)* 07.11.2003	Priority date *(day/month/year)* 08.11.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/18		
Applicant ABLYNX N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	22.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mueller, F Telephone No. +49 89 2399-7722

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE 03/00193

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-56, 58-65, 67-77	as originally filed
57, 66	received on 10.03.2004 with letter of 10.03.2004

Claims, Numbers

1-66	received on 04.02.2005 with letter of 02.02.2005

Drawings, Sheets

1/9, 2/9, 4/9-9/9	as originally filed
3/9	received on 10.03.2004 with letter of 10.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10,20,29,38,48

   because:

   ☒ the said international application, or the said claims Nos. 15,25,34,43,56 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10,20,29,38,48

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9,11-19,21-28,30-37,39-47,49-66
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9,11-19,21-28,30-37,39-47,49-66
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9,11-19,21-28,30-37,39-47,49-66
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

Sequence listings filed, 41 pages, with the letter of 10.03.04, are filed after the filing date of the application and do not form part of the description and will not be annexed to this communication/report (Rule 13ter (f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15,25,34,43 and 56 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67 (iv) PCT. Consequently no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

No international search report was established for the subject-matter of claims 10,20,29,38 and 48, see sheet 210 of the ISR. Therefore no opinion with respect to novelty, inventive step and industrial applicability will be formulated (Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
   D1: EP-A-0 952 218
   D2: WO 99/23221 A
   D3: ELS CONRATH K ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 10, 9 March 2000, pages 7346-7350,
   D5: Cortez-Retamozo et al., Int. J. Cancer, 98, 14.01.2002, pp.456-462

The document D5 was not cited in the international search report. A copy of the document is appended hereto.

2. The subject-matter of claim 1 is novel (Article 33(2) PCT).
   D1 describes bispecific antibodies which consist of a VH-VL construct, see e.g. claim 20. D1 therefore is considered not to interfere with the subject-matter of claim 1

which relates to a single domain antibody which devoid of light chains. Novelty can also be acknowledged for claim 66 (Article 33(2) PCT).

3. D2 and D3 describes multivalent single polypeptide antibodies of camel, see e.g. claims of D2, which are considered to belong to the class of single domain antibodies. D3 further discusses, by describing the same principal of designing bivalent antibodies construct (VHH, beta-lactamase, lysozyme) as in the present application, the plasma stability of the described bifunctional construct, see e.g. p.7350, 1. col., 2.par. ff. and p.7350 last par. The described antibodies are stable over 44h in mouse plasma, which were tested in vitro. The single domain antibodies fragments are cleared from the blood and an elimination half-life of 1.5-2 hr is calculated, see p. 7349, 2. col. 2. par with reference to V. Cortez-Retamozo et al., Int. J. Cancer, 98, 456-462, 14.01.2002 (D5), see p. 459, 1. col., 1. par.

   The present application refers to an increased presence of the claimed single domain antibody constructs in mouse sera, which were tested in in vivo experiments, see p. 63 and Figures 8-11. The claimed antibodies are therefore useful in therapeutic and diagnostic applications. An inventive step for claims 1-9,11-19,21-28,30-37,39-47,49-66 could therefore be acknowledged (Article 33(3) PCT).

4. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor is/are this/these document/s identified therein.

Re Item VIII
Certain observations on the international application

Claims 12-15,22-25,31-34,40-45,50-56 refer to two different categories (product and use). Article 6 PCT is thus not fulfilled for these claims.

modifications in this dosage range may be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein. See Remington's Pharmaceutical Sciences (Martin, E.W., ed. 4), Mack Publishing Co., Easton, PA. The dosage can also be adjusted by the individual physician in the event of any complication.

EXAMPLES

Example 1: Immunization of llamas

One llama was immunized with human serum albumin (HSA). The immunization scheme is summarized in Table 1.

Example 2: Repertoire cloning

Peripheral blood lymphocytes (PBLs) were isolated by centrifugation on a density gradient (Ficoll-Paque Plus Amersham Biosciences). PBLs were used to extract total RNA (Chomczynski and Sacchi 1987). cDNA was prepared on 100 µg total RNA with MMLV Reverse Transcriptase (Gibco BRL) using oligo d(T) oligonucleotides. The cDNA was purified with a phenol/chloroform extraction, followed by an ethanol precipitation and subsequently used as template to amplify the VHH repertoire.

In a first PCR, the repertoire of both conventional (1.6 kb) and heavy-chain (1.3 kb) antibody gene segments were amplified using a leader specific primer (5' - GGCTGAGCTCGGTGGTCCTGGCT- 3') (SEQ ID N° 41) and the oligo d(T) primer (5'-AACTGGAAGAATTCGCGGCCGCAGGAATTTTTTTTTTTTTTTTT-3') (SEQ ID N° 42). The resulting DNA fragments were separated by agarose gel electrophoresis and the 1.3 kb fragment, encoding heavy-chain antibody segments was purified from the agarose gel. A second PCR was performed using a mixture of FR1 reverse primers and the same oligo d(T) forward primer. The PCR products were digested with *SfiI* (introduced in the FR1 primer) and *BstEII* (naturally occurring in FR4). Following gel electrophoresis, the DNA fragment of approximately 400 basepairs were purified from gel and ligated into the corresponding restriction sites of phagemid pAX004 to obtain a library of cloned VHHs after electroporation of *Escherichia coli* TG1. The size of the library was 1.4 x 10^7 cfu, and all clones contained insert of the correct size.

Example 27: Functionality of both VHHs in the bispecific construct

A microtiterplate was coated with 5 µg/ml mouse serum albumin overnight at 4°C. After washing the plate, wells were blocked for 2 hours with PBS-1% casein. The bispecific proteins were allowed to bind to the wells for 2 hours at RT. After washing, human, dog and pig plasma was added at different dilutions and allowed to bind for 2 hours at RT. Binding of vWF was detected with anti-vWF-HRP from DAKO at 1/3000 dilution. Staining was performed with ABTS/H_2O_2. Results are shown in Figure 14 and indicate that functionality of both VHHs is retained in the bispecific construct.

Example 28: Inhibition of binding of vWF to collagen by the bispecific constructs as compared to the monovalent VHHs

Inhibition for binding of vWF to collagen was tested for monovalent as compared to bispecific constructs as described in Example 20. IC50 values are summarized in Table 11. Results indicate that the inhibitory properties of the VHH are retained in the bispecific construct.

Example 29: Construction of a bispecific construct containing a VHH-CDR3 fragment fused to an anti-serum albumin VHH

A functional portion, the CDR3 region of MP2F6SR, was amplified by using a sense primer located in the framework 4 region (F6 CRD3 Forward:CTGGCCCCAGAAGTCATACC) (SEQ ID N° 43) and an anti-sense primer located in the framework 3 region (F6 CDR3 Reverse primer:TGTGCATGTGCAGCAAACC) (SEQ ID N° 44).

In order to fuse the CDR-3 fragment with the anti-serum albumin VHH MSA-21, a second round PCR amplification was performed with following primers:

F6 CDR3 Reverse primer Sfi1:

GTCCTCGCAACTGCGGCCCAGCCGGCCTGTGCATGTGCAGCAAACC (SEQ ID N° 45)

F6 CDR3 Forward primer Not1:

GTCCTCGCAACTGCGCGGCCGCCTGGCCCCAGAAGTCATACC (SEQ ID N° 46)

The PCR reactions was performed in 50 ml reaction volume using 50pmol of each primer. The reaction conditions for the primary PCR were 11 min at 94 °C, followed by 30/60/120 sec at 94/55/72 °C for 30 cycles, and 5 min at 72°C. All reaction were performed wit 2.5 mM MgCl2 , 200 mM dNTP and 1.25U AmpliTaq God DNA Polymerase (Roche Diagnostics, Brussels, Belgium).

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AMENDED CLAIMS (amendments indicated)

1. A polypeptide construct comprising:
- at least one single domain antibody directed against a therapeutic and/or diagnostic target, and

- at least one single domain antibody directed against a serum protein.

2. A polypeptide construct according to claim 1 wherein:
- the number of anti-target single domain antibodies is at least two, and
- at least two anti-target single domain antibodies do not share the same sequence, or all the anti-target single domain antibodies share the same sequence.

3. A polypeptide construct according to claim 1 wherein:
- the number of anti-serum protein single domain antibodies is at least two, and
- at least two anti-serum-protein single domain antibodies do not share the same sequence, or all the anti-serum-protein single domain antibodies share the same sequence.

4. A polypeptide construct according to any of claims 1 to 3 wherein at least one single domain antibody is a *Camelidae* VHHs antibody.

5. A polypeptide construct according to any of claims 1 to 4 wherein at least one single domain antibody is a humanised *Camelidae* VHHs antibody.

6. A polypeptide construct according to any of claims 1 to 5 wherein said serum protein is any of serum albumin, serum immunoglobulins, thyroxine-binding protein, transferring, or fibrinogen or a fragment thereof.

7. A polypeptide construct according to claim 1 to 6 wherein a single domain anti-serum protein antibody correspond to a sequence represented by any of SEQ ID NOs: 1 to 4, and 28 to 40.

8. A polypeptide construct according to any of claims 1 to 7 wherein a target is TNF-alpha-alpha.

9. A polypeptide construct according to claim 7 corresponding to the sequence represented by any of SEQ ID NO: 5 to 18.

10. A polypeptide construct according to any of claims 8 to 10, wherein said polypeptide construct is a homologous sequence of said polypeptide construct, a functional portion of said polypeptide construct, or an homologous sequence of a functional portion of said polypeptide construct.

11. A nucleic acid encoding a polypeptide construct according to any of claims 8 to 10.

12. A polypeptide construct according to any of claims 8 to 10, or a nucleic acid according to claim 11 for use in the treatment, prevention and/or alleviation of disorders relating to inflammatory processes.

13. Use of a polypeptide construct according to any of claims 8 to 10, or a nucleic acid according to claim 11 for the preparation of a medicament for the treatment, prevention and/or alleviation of disorders relating to inflammatory processes.

14. A polypeptide construct or nucleic acid according to claim ~~13~~ 12 or a use of a polypeptide construct or nucleic acid according to claim 13 wherein said disorders are any of rheumatoid arthritis, Crohn's disease, ulcerative colitis and multiple sclerosis.

15. A polypeptide construct or nucleic acid according to claims 12 and 14 or a use of a polypeptide construct according to claim 13 and 14 wherein said polypeptide construct is administered intravenously, orally, sublingually, topically, nasally, vaginally, rectally, subcutaneously or by inhalation.

16. A polypeptide construct according to any of claims 1 to 7 wherein a target is vWF

17. A polypeptide construct according to claims 1 to 7 wherein a target is collagen.

18. A polypeptide construct according to claim 16 wherein at least one anti-target single domain antibody is anti-vWF VHHs.

19. A polypeptide construct according to claim 18 corresponding to the sequence represented by any of SEQ ID NOs: 19 to 21.

20. A polypeptide construct according to any of claims 16 to 19, wherein said polypeptide construct is a homologous sequence of said polypeptide construct, a functional portion of

said polypeptide construct, or an homologous sequence of a functional portion of said polypeptide construct.

21. A nucleic acid encoding a polypeptide construct according to any of claims 16 to 20.

22. A polypeptide construct according to any of claims 16 to 20, or a nucleic acid according to claim 21 for use in the treatment, prevention and/or alleviation of disorders or conditions relating to platelet-mediated aggregation or dysfunction thereof.

23. Use of a polypeptide construct according to any of claims 16 to 20, or a nucleic acid according to claim 21 for the preparation of a medicament for the treatment, prevention and/or alleviation of disorders or conditions relating to platelet-mediated aggregation or dysfunction thereof.

24. A polypeptide construct or nucleic acid according to claim 22 or a use of a polypeptide construct or nucleic acid according to claim 23 wherein said disorders are any of cerebral ischemic attack, unstable angina pectoris, cerebral infarction, myocardial infarction, peripheral arterial occlusive disease, restenosis, and said conditions are those arising from coronary by-pass graft, or coronary artery valve replacement and coronary interventions such angioplasty, stenting, or atherectomy.

25. A polypeptide construct or nucleic acid according to claims 22 and 24 or a use of a polypeptide construct according to claim 23 and 24 wherein said polypeptide construct is administered intravenously, orally, sublingually, topically, nasally, vaginally, rectally, subcutaneously or by inhalation.

26. A polypeptide construct according to any of claims 1 to 7 wherein a target is IgE.

27. A polypeptide construct according to claim 26 wherein at least anti-target single domain antibody is anti-IgE VHHs.

28. A polypeptide construct according to claim 26 corresponding to the sequence represented by any of SEQ ID NOs: 22 to 24.

29. A polypeptide construct according to any of claims 26 to 28, wherein said polypeptide construct is a homologous sequence of said polypeptide construct, a functional portion of

said polypeptide construct, or an homologous sequence of a functional portion of said polypeptide construct.

30. A nucleic acid encoding a polypeptide construct according to any of claims 26 to 29.

31. A polypeptide construct according to any of claims 26 to 29, or a nucleic acid according to claim 30 for use in the treatment, prevention and/or alleviation of disorders or conditions relating to allergic reactions.

32. Use of a polypeptide construct according to any of claims 26 to 29, or a nucleic acid according to claim 30 for the preparation of a medicament for the treatment, prevention and/or alleviation of disorders or conditions relating to allergic reactions.

33. A polypeptide construct or nucleic acid according to claim 31 or a use of a polypeptide construct or nucleic acid according to claim 32 wherein said disorders are any of hay fever, asthma, atopic dermatitis, allergic skin reactions, allergic eye reactions and food allergies.

34. A polypeptide construct or nucleic acid according to claims 31 and 33 or a use of a polypeptide construct according to claim 32 and 33 wherein said polypeptide construct is administered intravenously, orally, sublingually, topically, nasally, vaginally, rectally, subcutaneously or by inhalation.

35. A polypeptide construct according to any of claims 1 to 7 wherein a target is IFN-gamma.

36. A polypeptide construct according to claim 35 wherein at least one anti-target single domain antibody is anti-IFN-gamma VHHs.

37. A polypeptide construct according to claim 35 corresponding to a sequence represented by SEQ ID NOs: 25 to 27.

38. A polypeptide construct according to any of claims 35 to 37, wherein said polypeptide construct is a homologous sequence of said polypeptide construct, a functional portion of said polypeptide construct, or an homologous sequence of a functional portion of said polypeptide construct.

39. A nucleic acid encoding a polypeptide construct according to any of claims 35 to 38.

40. A polypeptide construct according to any of claims 35 to 38, or a nucleic acid according to claim 39 for use in the treatment, prevention and/or alleviation of disorders or conditions wherein the immune system is over-active.

41. Use of a polypeptide construct according to any of claims 35 to 38, or a nucleic acid according to claim 39 for the preparation of a medicament for the treatment, prevention and/or alleviation of disorders or conditions wherein the immune system is over-active.

42. A polypeptide construct or nucleic acid according to claim 40 or a use of a polypeptide construct or nucleic acid according to claim 41 wherein said disorders are any of Crohn's disease, autoimmune disorders and organ plant rejection in addition inflammatory disorders such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and multiple sclerosis.

43. A polypeptide construct or nucleic acid according to claims 40 and 42 or a use of a polypeptide construct according to claim 41 and 42 wherein said polypeptide construct is administered intravenously, orally, sublingually, topically, nasally, vaginally, rectally, subcutaneously or by inhalation.

44. A composition comprising a polypeptide construct according to any of claims 8 to 10, 12, 14 and 15, or a nucleic acid encoding said polypeptide construct and a pharmaceutically acceptable vehicle.

45. A composition comprising a polypeptide construct according to any of claims 16 to 20, 22, 24 and 25, or a nucleic acid encoding said polypeptide construct and a pharmaceutically acceptable vehicle.

46. A composition comprising a polypeptide construct according to any of claims 26 to 29, 31, 33 and 34, or a nucleic acid encoding said polypeptide construct and a pharmaceutically acceptable vehicle.

47. A polypeptide construct according to any of claims 1 to 7 directed against a single target wherein said target is involved in a disease process.

48. A polypeptide construct according to claim 47, wherein said polypeptide construct is a homologous sequence of said polypeptide construct, a functional portion thereof, of an homologous sequence of a functional portion thereof.

49. A nucleic acid encoding a polypeptide construct according to claims 47 and 48.

50. A polypeptide construct according to claims 47 and 48, or a nucleic acid according to claim 49 for use in the treatment, prevention and/or alleviation of disorders or conditions in which the target is involved.

51. Use of a polypeptide construct according to any of claims 47 and 48, or a nucleic acid according to claim 49 for the preparation of a medicament for the treatment, prevention and/or alleviation of disorders or conditions in which the target is involved.

52. A polypeptide construct according to claims 48 and 50, or a nucleic acid according to claim 49 for use in treating, preventing and/or alleviating the symptoms of a disease requiring a therapeutic or diagnostic compound which is not rapidly cleared from the circulation.

53. Use of a polypeptide construct according to any of claims 48 and 50, or a nucleic acid according to claim 49 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of a disease requiring a therapeutic or diagnostic compound which is not rapidly cleared from the circulation.

54. A polypeptide construct according to any of claims 48 and 50, or a nucleic acid according to claim 49 for use in treating, preventing and/or alleviating the symptoms of a disease requiring a therapeutic or diagnostic compound which remains active in the circulation for extended periods of time.

55. Use of a polypeptide construct according to any of claims 48 and 50, or a nucleic acid according to claim 49 for the preparation of a medicament for treating, preventing and/or alleviating the symptoms of a disease requiring a therapeutic or diagnostic compound which is remains active in the circulation for extended periods of time.

56. A polypeptide construct or nucleic acid according to any of claims 50, 52, 54, or use of a polypeptide construct or nucleic acid according to any of claims 51, 52, 53, 55, wherein said

polypeptide construct is administered intravenously, orally, sublingually, topically, nasally, vaginally, rectally, subcutaneously or by inhalation.

57. A composition comprising a polypeptide construct according to any of claims 1 to 7, 47, 48, 50, 52, 54 and 56, or a nucleic acid according to any of claims 49, 50, 52, 54 and 56 and a pharmaceutically acceptable vehicle.

58. A method of producing a polypeptide according to any of claims 1 to 10, 16 to 20 , 26 to 29, 47 and 48 comprising

(a) culturing host cells comprising nucleic acid capable of encoding a polypeptide according to any of claims 1 to 10, 16 to 20 , 26 to 29, 47 and 48, under conditions allowing the expression of the polypeptide, and,

(b) recovering the produced polypeptide from the culture.

59. A method according to claim 58, wherein said host cells are bacterial or yeast.

60. A method for prolonging the half-life of a single domain antibody in the blood stream of a subject, said antibody directed against a therapeutic and/or diagnostic target by joining thereto one or more single domain antibodies directed against a serum protein.

61. A method according to claim 60 wherein said anti-target single domain antibodies do not share the same sequence.

62. A method according to claim 60 wherein said anti-serum protein single domain antibodies do not share the same sequence.

63. A method according to claim 60 wherein said single domain antibodies are *Camelidae* VHH antibodies.

64. A method according to any of claims 60 to 63 wherein said serum protein is any of serum albumin, serum immunoglobulins, thyroxine-binding protein, transferring, or fibrinogen or a fragment thereof.

65. A method according to any of claims 60 to 64 wherein said serum protein comprises a sequence corresponding to any of SEQ ID NOs: 1 to 4, a homologous sequence, a functional portion thereof, or a homologous sequence of a functional portion thereof.

66. A composition comprising a polypeptide according to any of claims 1 to 7 or a nucleic acid capable of encoding said polypeptide and a pharmaceutically acceptable vehicle.

Figure 5

HindIII
1 aagcttgcat gcaaattcta tttcaaggag acagtcataa tgaaatacct attgcctacg gcagccgctg gattgttatt
M K Y L L P T A A A G L L L
< pelB-leader

SfiI *NcoI* *NotI* *PstI*
81 actcgc*ggcc* *cagccaggcca* tggggcctaa taggcggcag cacaggtgca gctgcaggag tcataatgag ggacccaggt
L A A Q P A M G P - - A A A Q V Q L Q E S - - G T Q V
Leader >< VHH#1 > < VHH#2

BstEII
161 caccgtctcc tcagaacaaa aactcatctc agaagaggat ctgaatgggg ccgcacatca tcatcatcat cattaatgag
T V S S E Q K L I S E E D L N G A A H H H H H H (SEQ ID N° 48)
>< C-MYC > < His6 >

EcoRI
241 aattcactgg ccg (SEQ ID N° 47)

Figure 6